DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 20 2004

Michael S. Labson
Elizabeth M. Walsh
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Covington & Burling
1201 Pennsylvania Ave., N.W.
Washington, D.C. 20004-2401

Re: Docket No. 2003P-0518/CP1

Dear Mr. Labson and Ms. Walsh:

This letter responds to your citizen petition dated November 5, 2003 (Petition), submitted on behalf of Wyeth Pharmaceuticals (Wyeth) concerning approval of abbreviated new drug applications (ANDAs) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), for sirolimus with Rapamune as the reference listed drug. You request that the Food and Drug Administration (FDA or Agency) refrain from approving any generic versions of Rapamune before April 11, 2006, which is the expiration date of the statutory exclusivity for protected information in the Rapamune labeling. Wyeth is the manufacturer of Rapamune.

For the reasons that follow, the Agency will not approve ANDAs for sirolimus based on omitting protected information in Rapamune labeling. Thus, your petition is granted.

I. BACKGROUND

A. Rapamune's Marketing Exclusivity

Rapamune (sirolimus) is an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients receiving renal transplants. FDA approved an oral solution formulation of Rapamune on September 15, 1999 (new drug application (NDA) 21-083), and a tablet formulation on August 25, 2000 (NDA 21-110). Both formulations are protected by new chemical entity exclusivity under section 505(c)(3)(D)(ii) of the Act until September 14, 2004. Rapamune was originally approved only for use in a regimen including cyclosporine and corticosteroids. However, over time, the combination of Rapamune and cyclosporine was found to be associated with increased renal function impairment. Wyeth conducted a clinical study providing evidence that the benefits of a cyclosporine withdrawal regimen outweighed the risks in patients at low to moderate risk of immune system reactions. The trial excluded high-risk patients. On April 11, 2003, based on this study, FDA approved efficacy supplements for both the oral solution and tablet formulations of Rapamune that provided for cyclosporine withdrawal procedures in patients at low to moderate risk for rejection. This new cyclosporine withdrawal labeling

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received 3 years of marketing exclusivity under section 505(c)(3)(D)(iv) of the Act, extending until April 11, 2006. The statutory exclusivity applies to both the oral solution and tablet formulations.

B. Rapamune's Current Labeling

Extensive information from the cyclosporine withdrawal clinical study has been included in the Rapamune labeling, including the *Pharmacokinetics*, *Clinical Studies*, *Indications and Usage*, *Warnings*, *Precautions*, and *Adverse Reactions* sections of the labeling. Following are some excerpts from the Rapamune labeling explaining the cyclosporine withdrawal regimen and safety profile.

The relevant portion of the *Indications and Usage* section of Rapamune labeling states:

> It is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune dose should be increased to reach recommended blood concentrations.... The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended.

Relevant portions of the *Precautions* section states:

> In patients at low to moderate immunologic risk ... continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients.... Renal function should be monitored during the administration of Rapamune in combination with cyclosporine. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels.

Rapamune's *Adverse Reactions* section states in part:

> **Rapamune following cyclosporine withdrawal:** ... [t]he incidence of hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

C. FDA's Authority to Approve an ANDA That Omits Labeling Protected by Exclusivity or Patent

The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]" and "information ... to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug..." (section 505(j)(2)(A)(i) and (v)). The Act provides the following two exceptions for when ANDA labeling may differ from that of the listed drug: (1) because changes reflect differences approved pursuant to an ANDA suitability petition or (2) because the drugs are produced or distributed by different manufacturers (section 505(j)(2)(A)(v)).

FDA regulations implementing the statutory exceptions to the same labeling requirement state that "... differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include ... omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act" (21 CFR 314.94(a)(8)(iv)). The regulations further provide, however, that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that the "... differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use" (21 CFR 314.127(a)(7)).[1]

II. DISCUSSION

You maintain that the Act and FDA regulations do not permit FDA to approve an ANDA for sirolimus that does not contain the cyclosporine withdrawal information because omitting that labeling would render the generic drug less safe than Rapamune (Petition at 2). You contend that the cyclosporine withdrawal information is essential to the safe and effective use of sirolimus because only a narrowly defined subset of high-risk patients are not covered by the labeling, and that even for those patients, the labeling information might help raise physicians' awareness of the risks of cyclosporine (id. at 4). You contend that without the cyclosporine withdrawal information in labeling, there would be potentially dangerous prescriber confusion, posing risks to all patients who receive treatment with sirolimus (id.).

FDA agrees that under § 314.127(a)(7), the Agency cannot approve an ANDA for a generic sirolimus product with labeling omitting the cyclosporine withdrawal language because that would make the product less safe and effective than Rapamune for its non-protected indication. As illustrated in section I.B above, the protected labeling in question contains extensive, critical prescribing information pertaining to cyclosporine withdrawal that any physician should receive to appropriately determine treatment for all indications for sirolimus. The data from the clinical study show that withdrawal of

[1] The Courts have upheld FDA's authority to approve generic drugs that omit labeling protected by exclusivity. *Bristol-Myers Squibb v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996) and *Sigma-Tau Pharmaceuticals, Inc.* v. Shwetz, 288 F.3d 141 (4th Cir. 2002).

cyclosporine can have a significant impact on the adverse event profile of patients on Rapamune therapy. The labeling warns that in low to moderate risk patients, sirolimus in combination with cyclosporine therapy beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of the combination for the individual patients. The continued use of cyclosporine with Rapamune is no longer an acceptable maintenance regimen in renal transplant recipients at low to moderate risk for rejection, a population that represents the majority of renal transplant patient recipients in the United States.

Furthermore, approving an ANDA for sirolimus without the cyclosporine withdrawal language, thereby limiting the indication to the remaining narrow subset of renal transplant patients at high risk for rejection, could be potentially unsafe and confusing. Information on the potential hazard of prolonged use of cyclosporine with sirolimus and the potential benefit of a cyclosporine-sparing regimen is needed to use the drug safely and effectively, even in the limited high-risk population. In particular, patients who were classified as high-risk because of their baseline characteristics, but who remain free of rejection episodes for 6 to 12 months post transplantation, may in fact be reclassified as low to moderate risk and conceivably could benefit from a cyclosporine-sparing regimen. In addition, information on such a regimen is necessary for prescribing physicians to titrate or individualize the graft recipient's immunosuppressive therapy.

Thus, FDA believes that it cannot approve an ANDA for a generic version of Rapamune that omits the protected cyclosporine withdrawal regimen information because this labeling is necessary to enable physicians to adequately assess the risks and benefits of sirolimus for the general population of renal transplants patients, including those at high risk. In other words, omission of the protected language would render the product less safe than Rapamune for the remaining, non-protected conditions of use.

III. CONCLUSION

For these reasons, your petition is granted. FDA will not approve an ANDA for sirolimus with Rapamune as the reference listed drug before the expiration of the statutory exclusivity of the cyclosporine withdrawal labeling on April 11, 2006.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research